EXHIBIT C

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

NOVOZYMES A/S, Plaintiff v. GENENCOR INTERNATIONAL, INC., and ENZYME DEVELOPMENT CORPORATION, Defendants	C.A. No. 05-160-KAJ

DECLARATION OF JOHN RICKERT DEVEREUX

I, John Rickert Devereux, do hereby declare as follows:

1. I am a citizen of the United States and am more than twenty-one (21) years of age.

2. I am a founder of Genentics Computer Group, Inc. ("GCG"), and was President of that company from 1990-1997. From 1997-2000, I was President and Chief Scientific Officer of GCG, when the company had been acquired by and was a wholly owned subsidiary of the Oxford Molecular Group, PLC.

3. Before I founded and worked for GCG, I was Assistant Director at the University of Wisconsin Biotechnology Center. Before that, I was a Project Coordinator in the University of Wisconsin Department of Genetics.

4. I have served on review panels for several government programs in molecular biology and genetics, including: DOE review panels for the Human Genome Program; NIH review panels for the Human Genome Program; the NIH/DOE Human Genome Joint

Informatics Task Force; the NIH/DOE Human Genome DNA Sequencing Work Group; and the National Center for Biotechnology Information, Board of Scientific Councilors.

5. I am an author or co-author of numerous publications, including several research publications in peer reviewed scientific journals. I am also a co-creator of the GCG Sequence Analysis Software Package, which is a collection of computer programs for the analysis of DNA and protein sequences. These programs include, *inter alia*, the GAP computer program that is discussed in detail in this Declaration.

6. Details of my education, professional experience and publications are included in the copy of my *Curriculum Vitae*, which is provided at Exhibit 1 of this Declaration.

I. BACKGROUND

7. I understand that this Declaration is being submitted in support of a law-suit between Novozymes A/S ("Novozymes"), and the parties Genencor International, Inc. ("Genencor") and Enzyme Development Corporation ("EDC"). In particular, I understand that Genencor and EDC have been accused of making and selling a product in the United States, called Spezyme Ethyl, that infringes U.S. Patent No. 6,867,031 entitled "AMYLASE VARIANTS" ("the '031 patent").

8. I have read and am familiar with the '031 patent. I also understand that this patent issued from an application that was first filed in 1995.

9. The subject matter of the '031 patent concerns variants of a certain kind of enzyme, called an alpha-amylase. The '031 patent states that the amino acid sequence of a "variant" alpha-amylase should be compared to the sequence of a "parent" alpha-amylase, to determine whether it has certain properties that are specified in the '031 patent. This section of

my declaration therefore describes some general principles for aligning and comparing amino acid sequences.

A. Alignment and Comparison of Amino Acid Sequences

10. When the amino acid sequences of two different proteins are compared to each other, they are first "aligned" to achieve the best juxtaposition. To achieve an optimal alignment, it is sometimes necessary to introduce one or more "gaps" into one or both of the amino acid sequences. An optimal alignment is an alignment that maximizes the number of matching amino acids in the two sequences, while also minimizing the number of mismatches and gaps.

11. Alignments of amino acid sequences can be made using well known computer programs. For example, the '031 patent, at 4:36-45,[1] refers to a computer program, called the "GAP" computer program, for aligning amino acid sequences. I am a creator of the GCG Sequence Analysis Package, which includes the GAP program. I am therefore familiar with this program.

12. It is also possible to assess the overall similarity between two amino acid sequences that have been aligned. One way in which this is done is to calculate the "percent identity" of the aligned sequences. The usual definition of percent identity calculates the number of amino acid residues in the alignment that are identical, divided by the total number of amino acid residues in the alignment. This definition considers *only* positions in an alignment where both sequences have an amino acid residue – *i.e.*, it considers only non-gap positions.

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[1] The convention used in this Declaration, when referring to a U.S. patent, is to cite column and line number(s) separated by a colon. In this case, when referring to the '031 patent, 4:36-45 refers to column 4, lines 36-45 of that document.

13. The '031 patent also describes using percent identity to assess the overall similarity between aligned sequences. In particular, the patent states that:

> [a]n amino acid sequence is considered to be X% homologous to the parent [alpha]-amylase if a comparison of the respective amino acid sequences, performed via known algorithms ... reveals an identity of X%.

See the '031 patent at 4:36-40. This corresponds to the definition, *supra*, for "percent identity."[2]

14. The '031 patent goes on to state that:

> [t]he GAP computer program from the GCG package, version 7.3 (June 1993), may suitably be used, employing default values for GAP penalties [Genetic Computer Group (1991), Programme Manual for the GCG Package, version 7, 575 Science Drive, Madison, Wis., USA 53711].

Id. at 4:40-45. Hence, the '031 patent identifies GAP as one program that can be used to align two amino acid sequences and determine their percent identity.

B. The GAP Computer Program

15. As mentioned above, I am a co-creator of the GCG Sequence Analysis Package that is cited in the '031 patent. I am therefore familiar with that package, and with the GAP computer program that is included therein. This program calculates an alignment of two amino acid sequences[3] that maximizes the number of matches between amino acid residues while, at the same time, minimizes the number of gaps in the alignment.

16. Hence, the GAP program takes, as input, two individual amino acid sequences, and generates an alignment of those two sequences. The program also generates various

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[2] The terms "percent identity" and "percent homology" are often used interchangeably to describe what is, strictly speaking, the percent identity. It is clear from the above-cited definition, that the '031 patent also uses these terms interchangeably. In particular, it is clear to me, from reading of the '031 patent, that this patent is using the term "percent homology" to describe what is, strictly speaking, the "percent identity" of two aligned amino acid sequences.

numbers indicating the degree of similarity between the two sequences. One of these numbers is a "percent identity" value that is calculated as described above.

17. GAP calculates the alignment using a "symbol comparison table" that is specified by a user, along with two parameters called the "gap weight", and the "length weight."[4] The symbol comparison table, gap weight and length weight are sometimes also called the "scoring matrix", the "gap penalty", and the "gap extension penalty", respectively. The program contains a default symbol comparison table that it normally uses to make an alignment, along with default values for the gap weight and length weight parameters. However, a user can also specify a different symbol comparison table, and/or different values for the gap weight and length weight parameters if desired.

18. The '031 patent refers to a particular "version" or release of the GCG package. In particular, the patent refers to "[t]he GAP computer program from the GCG package version 7.3". The '031 patent at 4:40-41. Version 7.3 of the GCG package is no longer sold or supported by GCG. However, other versions of the GCG package are publicly available. These more recent versions contain a copy of the GAP program that uses the same algorithm as found in version 7.3 to align amino acid sequences and calculate their percent identity.

19. The more recent versions of the GAP program use a different default symbol comparison table to align sequences, and also use different default values for the gap weight and length weight parameters. However, the more recent versions of the GCG package include a copy of the symbol comparison table that was used as default in version 7.3 of the GCG package.

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[3] The GAP computer program can also align two nucleotide sequences. For convenience, however, I discuss the program here in terms of aligning amino acid sequences.

[4] Collectively, these two parameters (*i.e.*, the gap weight and length weight parameters) are also called the "gap penalties."

A user can therefore, if desired, align sequences with the current version of GAP using what was the default symbol comparison table in version 7.3 of that program. The user can also align sequences with the current version of GAP using values for the gap weight and length weight parameters that were the default values in version 7.3 of that program. In so doing, the program will produce the same alignment and percent identity value that would have been obtained using the GAP computer program from the GCG package version 7.3, using that verion's default symbol comparison table and gap penalty values.

II. AMINO ACID SEQUENCE ALIGNMENTS

20. This section of my Declaration describes experiments that were performed by me, or by others working under my supervision and control, to compare amino acid sequences as described in the '031 patent. In particular, these experiments use the GAP computer program to align and compare the amino acid sequence of the Spezyme Ethyl product to SEQ ID NO:3 of the '031 patent.

A. The Alignment of Spezyme Ethyl to '031 Patent SEQ ID NO:3

21. I have been given a document, entitled "Spezyme Ethyl Amino Acid Sequence", which is attached to this Declaration as Exhibit 2. This document contains an amino acid sequence that is written using the standard, single-letter code for amino acid residues. I understand that this is the amino acid sequence of a protein found in the Spezyme Ethyl product.

22. I, or others working under my supervision and control, have aligned the amino acid sequence at Exh. 2 with SEQ ID NO:3 (as set forth in the '031 patent's Sequence Listing), and determined the percent identity between these two aligned sequences. The alignment was performed using the GAP program that is included in version 10 of the GCG package. However,

the program made the alignment using a symbol comparison table that was the default in version 7.3 of the GCG package. The gap penalty parameters (*i.e.*, the gap weight and length weight parameters) were also given values equal to what were their default values in the GAP program included with version 7.3 of the GCG package.

23. More specifically, the amino acid sequence of SEQ ID NO:3 from the '031 patent's Sequence Listing was transcribed into the single-letter amino acid code and saved into a computer file, named "NewB.pep", suitable for loading as input into the GAP computer program. The Spezyme Ethyl amino acid sequence (Exh. 2) was also saved into a file, named "SPEZE.pep", for loading into the GAP program. The amino acid sequences in these two files were uploaded into the GAP computer program, and aligned using the symbol comparison table "oldpep.cmp" that is included with version 10 of the GCG package. Gap Weight and Length Weight parameter values of 30 and 3, respectively, were used to make the alignment.

24. A copy of the output generated from the foregoing alignment is set forth in a document entitled "GAP ALIGNMENT: SEQ ID NO:3 to Spezyme Ethyl (Old Matrix)", which is attached to this Declaration as Exhibit 3. Inspection of this output reveals that residues 1-178 and 181-486 of the '031 patent's SEQ ID NO:3 align with residues 1-178 and 179-484, respectively, in the Spezyme Ethyl sequence. Gaps are introduced into the Spezyme Ethyl sequence at positions aligning with residues 179 and 180 in SEQ ID NO:3. Also, SEQ ID NO:3 contains an additional 31 amino acid residues at its carboxy terminus (*i.e.*, residues 487-514 in SEQ ID NO:3) that do not align with any residues in the Spezyme Ethyl sequence.

25. As explained above, the formula for percent identity does not consider gaps and/or non-aligning amino acid residues. When I consider the alignment at Exh. 3, I see (counting only non-gap positions) that there is a total of 484 amino acid residues in the

alignment. 479 of these 484 residues are identical. Hence, I find that the percent identity of these two sequences is 479/484 x 100% = 98.967%.[5] This is also the percent identity calculated by the GAP program. *See* Exh. 3 on page 1.

26. In addition, the Spezyme Ethyl sequence at Exh. 2 was also aligned to SEQ ID NO:3 of the '031 patent using the GAP program with the default symbol comparison table, and default gap weight and length weight parameter values for version 10 of the GCG package. Specifically, the files NewB.pep and SPEZE.pep, which contained the amino acid sequences of SEQ ID NO:3 and Spezyme Ethyl, respectively, were uploaded into the GAP computer program (version 10) and aligned using the default symbol comparison table "blosum62.cmp". Default Gap Weight and Length Weight parameter values of 8 and 2, respectively, were also used for this alignment.

27. A copy of the output generated is set forth in a document entitled "GAP ALIGNMENT: SEQ ID NO:3 to Spezyme Ethyl (New Matrix)", which is attached to this Declaration as Exhibit 4. Upon comparing this output to the output at Exhibit 3 (*i.e.*, the output from GAP using the default symbol comparison table and gap penalty values from version 7.3 of the GCG package), I find that the two alignments are identical. As in Exh. 3, residues 1-178 and 181-486 of the '031 patent's SEQ ID NO:3 align with residues 1-178 and 179-484, respectively, in the Spezyme Ethyl sequence. Gaps are introduced into the Spezyme Ethyl sequence at positions aligning with residues 179 and 180 in SEQ ID NO:3. Also, SEQ ID NO:3 contains an

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[5] As noted above, the percent-identity is calculated according to a formula that considers *only* positions in an alignment where both sequences have an amino acid residue – *i.e.*, it considers only non-gap positions. Hence, the calculation does not consider the gap aligning with residues 179-180 in SEQ ID NO:3. Nor does this standard calculation consider the 31 amino acid residues of the carboxy-terminus (*i.e.*, residues 487-514) of SEQ ID NO:3 that do not align with any residues of the Spezyme Ethyl sequence.

additional 31 amino acid residues at its carboxy terminus (*i.e.*, residues 487-514 in SEQ ID NO:3) that do not align with any residue in the Spezyme Ethyl sequence. There is a total of 484 amino acid residues in the alignment, of which 479 are identical. Hence, the percent identity is 479/484 x 100% = 98.967%. This is also the percent identity calculated by the GAP program. *See* Exh. 5 at page 1.

B. The Alignment of Spezyme Ethyl to '031 Patent Figure 1, Sequence 3

28. For the foregoing analysis, I have relied on the amino acid sequence of SEQ ID NO:3 that is set forth in the '031 patent's Sequence Listing. The '031 patent indicates that the amino acid sequence identified as sequence 3 in Figure 1 is also SEQ ID NO:3. *See* in the '031 patent at 29:38-45. However, there are in fact some differences between these two amino acid sequences.[6] These differences do not affect my analysis or conclusions, as explained in detail below.

29. In particular, the amino acid sequence identified as sequence 3 in Figure 1 of the '031 patent was transcribed into a computer file, named "NewA.pep". This file was used to align that sequence with the amino acid sequence of Spezyme Ethyl (Exh. 2) using the GAP computer program as described above. As before, two alignments were done. The first alignment was done using the GAP program with what were the default symbol comparison table and the default gap weight and length weight parameters in version 7.3 of the GCG package. The second alignment was done using GAP with the default symbol comparison table, and

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[6] I have compared SEQ ID NO:3 from the '031 patent's Sequence Listing to sequence 3 in Figure 1 of that patent. The differences between these two sequences are limited to the following ten amino acid substitutions: A73T, S217N, D250Y, M278T, N281D, T304A V416G, W492R, S493P, and D501G.

default gap penalty values of GCG package version 10. The resulting alignments are shown in documents entitled "GAP ALIGNMENT: Sequence 3 (Figure 1) to Spezyme Ethyl (Old Matrix)" and "GAP ALIGNMENT: Sequence 3 (Figure 1) to Spezyme Ethyl (New Matrix)", respectively. Copies of those documents are attached to this Declaration as Exhibits 5 and 6, respectively.

30. As with SEQ ID NO:3, residues 1-178 and 181-486 of the '031 patent's SEQ ID NO:3 align with residues 1-178 and 179-484, respectively, in the Spezyme Ethyl sequence. Gaps are introduced into the Spezyme Ethyl sequence at positions aligning with residues 179 and 180 in sequence 3 of the '031 patent's Figure 1. Also, sequence 3 in that Figure contains an additional 31 amino acid residues at its carboxy terminus (*i.e.*, residues 487-514 in sequence 3 of the '031 patent's Figure 1) that do not align with any residue in the Spezyme Ethyl sequence. There is a total of 484 amino acid residues in the alignment, of which 482 are identical. Hence, the percent identity is 482/484 x 100% = 99.587%. This is also the percent identity calculated by the GAP program, regardless of whether default parameters from GCG package version 7.3 (Exh. 5) or version 10 (Exh. 6) are used.

C. *Alignment of Spezyme Ethyl to the ATCC Alpha-Amylase*

31. I have also been given a document entitled "ATCC 31,195 Alpha-Amylase Amino Acid Sequence", which is attached to this Declaration as Exhibit 7. This document contains an amino acid sequence that is written using the standard, single-letter code for amino acid residues. I understand that this is the sequence of a recombinant protein expressed by the alpha-amylase gene from a natural isolate of *Bacillus stearothermophilus*. I understand that this natural isolate is available from the American Type Culture Collection ("ATCC") and has been

given the accession number ATCC 31,195. For convenience, therefore, the alpha-amylase from this isolate is referred to as the "ATCC 31,195 alpha-amylase".

32. I, or others working under my supervision and control, have aligned the ATCC 31,195 alpha-amylase sequence at Exhibit 7 with the Spezyme Ethyl amino acid sequence at Exhibit 2, and determined the percent identity between these two aligned sequences. As with the other sequence alignments, described *supra*, alignments were performed using the GAP program that is included in version 10 of the GCG package. Again, a first alignment was done using what were the default symbol comparison table, and default gap weight and length weight parameters in version 7.3 of the GCG package. A second alignment was done using the default symbol comparison table, and default gap penalty values of GCG package version 10.

33. More specifically, the ATCC 31,195 alpha-amylase sequence (Exh. 7) was saved into a file, named "NewC.pep" for loading into the GAP program. The amino acid sequence in this file was uploaded into the GAP computer program, along with the Spezyme Ethyl amino acid sequence (Exh. 2) contained in the file "SPEZE.pep". The amino acid sequences were then aligned by the GAP computer program using the symbol comparison table "oldpep.cmp" that is included with version 10 of the GCG package. Gap Weight and Length Weight parameter values of 30 and 3, respectively, were used to make the alignment. A copy of the output generated from this alignment is set forth in a document entitled "GAP Alignment: ATCC 31,195 Alpha-Amylase to Spezyme Ethyl (Old Matrix)", which is attached to this Declaration as Exhibit 8.

34. In a second alignment, the files NewC.pep and SPEZE.pep were uploaded into the GAP computer program (version 10) and aligned using the default symbol comparison table "blosum62.cmp". Default Gap Weight and Length Weight parameter values of 8 and 2, respectively, were also used for this alignment. A copy of the output generated from this

alignment is set forth in a document entitled "GAP Alignment: ATCC 31,195 Alpha-Amylase to Spezyme Ethyl (New Matrix)", which is attached to this Declaration as Exhibit 9.

35. Inspection of the outputs at Exhibits 8 and 9 reveals that the two alignments are identical. In both cases, residues 1-178 and 181-486 of the ATCC 31,195 alpha-amylase amino acid sequence (Exh. 7) align with residues 1-178 and 179-484, respectively, in the Spezyme Ethyl sequence (Exh. 2). Gaps are introduced into the Spezyme Ethyl sequence at positions aligning with residues 179 and 180 in the ATCC 31,195 alpha-amylase sequence. The ATCC 31,195 alpha-amylase sequence contains three additional amino acid residues at its C-terminus (*i.e.*, residues 487-489 in Exh. 7) that do not align with any residue in the Spezyme Ethyl sequence.

36. Counting only the non-gap positions in the alignments at Exhibits 8 and 9, I see that there is a total of 484 amino acid residues in both of these alignments. All of the aligning amino acid residues are identical in the two proteins. Hence, the percent identity of these two sequences is 100% (*i.e.*, 484/484 x 100%). *See* Exhs. 8 and 9.

37. The alignments of the Spezyme Ethyl amino acid sequence are shown together in Exhibit 10 of this Declaration. In particular, the amino acid sequence on the top line at Exh. 10, which is labeled "Spezyme Ethyl", shows the Spezyme Ethyl amino acid sequence at Exhibit 2. The second and third lines of Exh. 10 are labeled "SEQ ID NO:3" and "Fig. 1, Seq. 3", respectively, and show the amino acid sequences of SEQ ID NO:3 and of Figure 1, Sequence 3 in the '031 patent. Each of these sequences is aligned to the Spezyme Ethyl amino acid sequence as shown in Exhibits 3-4 (for alignments of SEQ ID NO:3 and Spezyme Ethyl) and in Exhibits 5-6 (for the alignments of Figure 1, Sequence 3 and Spezyme Ethyl). The last line at Exhibit 10

is labeled "ATCC 31,195", and shows the alpha-amylase amino acid sequence of that strain (Exh. 7) aligned with Spezyme Ethyl as shown in Exhibits 8-9.

38. A gap of two amino acid residues occurs in the Spezyme Ethyl amino acid sequence (Exh. 10, line 1) that does not occur in any of the other amino acid sequences. This gap is highlighted, to make it more easily seen in Exhibit 10. The gap aligns with residues 179-180 in SEQ ID NO:3 of the '031 patent (Exh. 10, line 2), and also aligns with residues 179-180 in sequence 3 of Figure 1 in that patent (Exh. 10, line 3). This gap also aligns with residues 179-180 in the ATCC 31,195 alpha-amylase amino acid sequence (Exh. 10, line 4).

39. The very high level of similarity between these amino acid sequences is also apparent from visual inspection of Exhibit 10. As mentioned above, 479 out of 484 amino acid residues are identical in the alignment of Spezyme Ethyl to SEQ ID NO:3. In other words, only five amino acid residues in the alignment of SEQ ID NO:3 differ from amino acid residues in the Spezyme Ethyl sequence. Similarly, only two amino acid residues in the alignment of sequence 3 from the '031 patent's Figure 1 (Exhibit 10, line 3) differ from amino acid residues in the Spezyme Ethyl sequence. These amino acid residues are highlighted, to make them more readily seen in Exhibit 10.

40. The Spezyme Ethyl amino acid sequence is even more similar to that of the ATCC 31,195 alpha-amylase. In particular, and as explained above, *all* of the aligning residues are identical in these two proteins (*i.e.*, they have 100% identity). Spezyme Ethyl differs from the alpha-amylase of the ATCC 31,195 isolate *only* by (a) the gap aligning with residues 179-180, and (b) the three additional amino acid residues at the ATCC 31,195 alpha-amylase's C-terminus. I find that, apart from these simple differences, the two sequences are *entirely* identical.

III. CONCLUSION

41. From the foregoing, I find that the amino acid sequence of Spezyme Ethyl's alpha-amylase (Exh. 2) has more than 95% identity to SEQ ID NO:3 of the '031 patent, and contains a deletion of the amino acids aligning with positions 179 and 180 of the '031 patent SEQ ID NO:3. These results are independent of the symbol comparison table and gap penalty parameters used to align the two sequences. Moreover, I reach the same conclusion regardless of whether Spezyme Ethyl is aligned to SEQ ID NO:3 of the '031 patent's sequence listing, or to the amino acid sequence identified as sequence 3 in '031 patent Figure 1.

42. I also find that the amino acid sequence of Spezyme Ethyl's alpha-amylase (Exh. 2) has more than 95% identity to the ATCC alpha-amylase amino acid sequence at Exhibit 7. Again, these results are independent of the symbol comparison table and gap penalty parameters used to align the two sequences.

43. I declare under penalty of perjury pursuant to the laws of the United States of America that the foregoing statements are true and correct.

Respectfully submitted,

Dated: June 11, 2005

John Rickert Devereux, Ph.D.

Attachments:

Exhibit 1: *Curriculum Vitae* of John Rickert Devereux;

Exhibit 2: Spezyme Ethyl Amino Acid Sequence;

Exhibit 3: GAP ALIGNMENT: SEQ ID NO:3 to Spezyme Ethyl (Old Matrix);

Exhibit 4: GAP ALIGNMENT: SEQ ID NO:3 to Spezyme Ethyl (New Matrix);

Exhibit 5: GAP ALIGNMENT: Sequence 3 (Figure 1) to Spezyme Ethyl (Old Matrix);

Exhibit 6: GAP ALIGNMENT: Sequence 3 (Figure 1) to Spezyme Ethyl (New Matrix);

Exhibit 7: ATCC 31,195 Alpha-Amylase Amino Acid Sequence;

Exhibit 8: GAP ALIGNMENT: ATCC 31,195 Alpha-Amylase to Spezyme Ethyl (Old Matrix);

Exhibit 9: GAP ALIGNMENT: ATCC 31,195 Alpha-Amylase to Spezyme Ethyl (New Matrix);

Exhibit 10: Alpha-Amylase Alignments